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Psychiatric Genetics

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PSYCHIATRIC GENETICS[1]

The recent intellectual and scientific achievements of evolutionary and molecular biology have had a profound influence on American psychiatry. New perspectives have emerged and doctrinaire approaches have yielded to interdisciplinary dialogue and research. A new generation of psychiatrists, educated in biochemistry and population biology, is beginning to explore the experimental and theoretical implications of behavior genetics research. Once resisted or ignored, the possibility of genotypic influences on human behavior now commands increasing attention in the behavioral, medical, and social sciences.

Psychiatric genetics, a subspecialty of human behavior genetics, is concerned with the genetic and environmental bases of behavioral disorder. This vast literature is rapidly expanding and no exhaustive review will be attempted here. Rather, certain areas relevant to contemporary psychiatric practice will be examined and some of the possible issues with which future research may be concerned will be underscored. Recent reviews may be consulted for a more comprehensive bibliography of the behavioral and psychiatric' genetics literature.

Man and Evolution

Man is a product of biological evolution. Gene variations introduced into

the human gene pool by mutation are shaped, primarily by natural selection, into integrated or coadapted gene complexes that promote the various individual and species adaptations to the range of environments in which man lives. Recent studies have shown that considerable genetic variation is present in the human gene pool. The Mendelian laws governing the transmission of the genetic material from parents to offspring facilitate the maintenance of this variation and ensure the biological uniqueness of virtually every individual.

Man is also a product of cultural evolution. His ability to acquire and transmit culture is among the distinctive characteristics inherent in man's genetic potential. Biological change over time is generally slow whereas change obtained through cultural evolution may be rapid and can transcend the limitations of both space and generations. Man has evolved and continues to evolve on both the biological and cultural levels; the two are in continuous interaction. Man's biological capacities have influenced the development and direction of his cultural history. Conversely, through his patterns of mating and his technology, culture affects man's biological evolution. A persisting problem in psychiatric genetics research is the separation of cultural and biological influences on human behavioral variation.

Genetic Determination of Behavior

Each human individual constitutes a system whose behavioral, morphological, and physiological characteristics are determined by gene-directed biological processes. The constellation of genes the individual carries, his *genotype,* exerts influences on behavior through its effects on development and on metabolic processes. The genotype, however, does not operate in a vacuum. Directly or indirectly, the intra- and intercellular milieu and other environmental factors modulate gene function. The genotype interacts with the environment to produce the *phenotype,* the visible or measurable characteristics of the individual.

Although genes are a determinant of behavior, genes do not *cause* behavior. Operationally, the genotype might be thought of as one of several variables that alter the probability that a given behavior will occur under certain environmental conditions. For example, male mice will fight each other, but some strains of mice are genotypically more predisposed to fight than others. Castrated animals of such strains are generally docile. Likewise, group-reared animals tend to be less aggressive than those reared in isolation. Thus the agonistic behavior observed between two male mice depends on many variables: the "right" genotype, gonadal status, previous social environment, and other biological and situational contingencies. None of these variables is a sufficient *cause* of the observed behavior, yet each plays a necessary role in determining the behavioral outcome.

One of the legacies of the nature-nuture controversy is the persisting confusion between the concepts of genotype and phenotype. The genotype of the individual is fixed at fertilization and, barring somatic mutations, persists throughout life.[2] Certain aspects of the phenotype, on the other hand, may change considerably, whereas, other aspects (e.g., temperament, response dispositions, etc.) may remain relatively stable over long periods of time. Inferences about the underlying genotypic determination drawn solely from the relative plasticity or stability of the phenotype may be misleading. The presence of phenotypic flexibility does not rule out the possibility of large genotypic contributions. Indeed, the capacity for phenotypic change may itself be genotypically determined. On the other hand, the maintenance of relatively enduring traits could be due to nongenetic factors. For example, intermittent schedules of reinforcement are capable of maintaining behavioral responses over long periods of time. Even grossly maladaptive behavior, involving self-punitive and self-injurious responses, can be maintained by reinforcement contingencies associated with the behavior and its consequences for the organism.

In the past, the tendency to associate genotypic influences on behavior with developmental determinism created misunderstanding of the goals of human behavior genetics and impeded substantive research. Some writers have implied that there are immutable states and fixed behavioral patterns blueprinted in the genome and manifested irrespective of environmental

contingencies. Evidence from animal research does not support this implication. Moreover, the relationship between genes and behavior is far more complex and in no way analogous to the relationship between a blueprint and the structure it represents. Behavior does not arise inexorably as a consequence of primary gene action; rather, it develops as a result of the joint interaction between genes and environment. The same genotype may respond differently when subjected to differential environmental treatments. The extent to which a genotype is affected phenotypically by environmental differences is a measure of the *norm of reaction* or reaction range of that genotype. The reaction range of a given genotype may be relatively broad or narrow; the fact that a reaction range exists permits environmental manipulations to be used in the modification and treatment of genetically determined disorders. For example, phenylketonuria is a hereditary disorder involving a deficiency of the hepatic enzyme, phenylalanine hydroxylase; untreated individuals may be severely retarded mentally. Early dietary intervention, however, often prevents the extreme intellectual deficits associated with this disorder. The demonstration of a genotypic influence on behavior in no way implies behavioral destiny.

Fundamentals of Genetics

Genes are the basic units of heredity. At fertilization, each human individual receives a complement of genes from each parent. These genes are

arranged linearly along the chromosomes, normally twenty-three pairs in number. All of the cells composing the individual derive from the fertilized egg and almost all carry a full complement of chromosomes. Through the process of meiosis, during gametogenesis, sex cells are formed, each carrying normally one representative of each chromosome pair. Occasionally, errors occur and a pair of homologous chromosomes fail to separate properly. Fertilization of gametes, which are formed when such nondisjunctional events occur, may thus produce a zygote lacking a given chromosomal pair (e.g., 45,XO) or with an additional chromosome (e.g., 47,XXY).

Genes are units of deoxyribonucleic acid (DNA). The DNA molecule consists of regularly alternating chains of phosphates and deoxyribose sugar groups to which pairs of nitrogenous bases are attached. The sequence of these bases determines the functional specificity of a gene. A sequence of three successive base pairs constitutes a triplet or coding unit for one of the twenty amino acids, the building blocks of a polypeptide chain. Alterations of the sequence of base pairs due to mis- copying, deletions, duplications, and the like, constitute *mutations.*

DNA acts as a template for the building of protein chains. This process involves the synthesis of a complementary chain of messenger ribonucleic acid (mRNA) that passes from the nucleus to the cytoplasm. In the cytoplasm, the mRNA chains attach themselves to ribsomes where amino acids,

conveyed individually by a second species of RNA, transfer RNA (tRNA), are attached together sequentially to construct the polypeptide chain.

Genes also regulate the rates of synthesis of the enzymes that direct the metabolic events of the organism. How gene action is regulated in higher organisms is not yet understood. Gene regulatory mechanisms underlie the processes of embryological development and tissue differentiation. Elucidation of these mechanisms may have important implications for our understanding of the relationship between genes and behavior. Hormones, for example, have profound effects on cellular differentiation and function. A possible hormonal influence on cellular differentiation, with long- lasting behavioral consequences, is the sexual differentiation of the central nervous system, in either a female or a male direction. This early differentiation occurs during a sensitive period of development and has been shown to influence the reproductive physiology as well as the organism's later behavior as an adult. The role of gene activation and/or repression in this process is likely.

Modes of Inheritance

In the first edition of the *Handbook,* Kallmann provided an extensive discussion of the modes of inheritance of genes with major phenotypic effects and of the methods generally employed in psychiatric genetics research. Since behavior is produced and maintained by multiple developmental and

physiological processes, each presumably directed by many genes, it is not surprising that the genetic transmission of most behavioral traits does not follow simple Mendelian modes of inheritance. Most behavioral variation is quantitative in nature.

Variation in quantitative characters is assumed to result from the joint action of many genes, each presumably with small phenotypic effect, and of environmental factors. The aim of a genetic analysis of quantitative characters is to determine the proportion of total phenotypic variation attributable to genetic causes.

Within populations, differences between individuals with respect to a given character are to varying degrees genotypic and/or environmental in origin. This phenotypic variation (V_P) generally expressed in terms of variances, is composed of a genotypic (V_G) and environmental (V_E) component; $V_P = V_G + V_E$. V_G may be further subdivided into V_A, the variance derived from the additive effects of genes and V_D, a nonadditive component, resulting from dominance. Other components of V_G representing respectively the effects of assortative or nonrandom mating and of epistasis, the interaction of genes at different loci, are sometimes present, but these will not be considered here. Estimates of the variance components may be obtained from the degree of similarity or correlation between relatives with respect to the character being studied. In practice, regression coefficients are used. A

more detailed treatment of quantitative genetics may be found in Falconer.

In the absence of dominance and environmental effects, the expected correlation between two relatives reflects the average number of genes they share in common. Thus, the expected correlation between a first degree relative and an index case (= proband) would be 0.5, since, on average, they share half their genes in common. For second degree relatives, who share on average one quarter of their genes in common, the expected correlation would be 0.25. The correlation between parent and offspring *($r_{p/o}$* can be shown to yield an estimate of *½ V_A/V_P* and that between sibs *($r_{s/s}$)* an estimate of *(½ V_A + ¼ V_D)/V_P*.

VA is the major cause of resemblance between relatives. If $r_{p/o}$ and $r_{s/s}$ are both about 0.5 as, for example, in the measure of total fingerprint ridge count, it suggests that most, if not all, of the variation can be accounted for simply by additive polygenic inheritance. When the correlations between first degree relatives are less than 0.5, additive variation is reduced and dominance and/or environmental contributions to V_P are increased. For example, $r_{p/o}$ and $r_{s/s}$ for systolic blood pressure are about 0.24 and 0.33 respectively. The components of variance may be calculated as follows: $V_A = 2r_{p/o} = 0.48$ and $V_D = 4(r_{s/s} - r_{p/o}) = 0.36$. Thus about 84 percent of the total variation in this character appears to be genotypic in origin with V_E accounting for 16 percent of the total. The relative proportion of the

phenotypic variance due to genotypic factors *(V_G/V_P)* defines the *degree of genetic determination*; in the previous example V_G/V_P = 84 percent. Since the additive genetic variation is an index of the degree of resemblance between relatives, a more informative measure is VA/V_P, which is called *heritability* and is symbolized h_2. Heritability, which represents the proportion of the phenotypic variance attributable to additive genetic variation, is of particular interest to the animal and plant breeder since it provides a measure that can be used to predict short-term gains in selective-breeding programs. In the example above h^2 = 48 percent.

V_E may sometimes be partitioned into subcomponents representing the between and within family environmental variation and the variation arising from ethnic and social class differences. Another source of variation arises from genotype-environment interactions, the differential responses of genotypes to different environments. For example, animals selectively bred for low error scores in a maze may, in an ordinary environment, outperform animals bred for high error scores. In an impoverished environment, however, the former may perform no better than the latter.

Two points need to be stressed. First, in the estimation of h^2 and of the components of V_P, it is assumed that heredity and environment are not correlated. This assumption may not be totally warranted since genotype and environment are often found to be correlated in studies of human behavior.

For example, an individual may receive genes from his parents predisposing him to schizophrenia, but he may also be reared in a disordered family environment that in itself may promote the production of psychopathology. Under these conditions it is difficult to distinguish between genotypic contributions and environmental ones. Second, estimates of h^2 should be interpreted with caution; h^2 is a population metric that ". . . tells us only about the ratio of the *prevailing* individual genetic differences to the prevailing individual environmental differences and cannot, in general, be extrapolated to other populations or other environments." For example, although the heritability of human stature is high, average height has changed substantially over the past century as a consequence of environmental changes. Thus, even where heritability measurements suggest little environmental influence, large environmental effects may be observed.

Threshold Characters

Some phenotypic characters, such as cleft lip and palate, diabetes, pyloric stenosis, talipes equinovarus, and other conditions appear to share both continuous and all-or-none characteristics. The inheritance of such characters might be best understood in terms of a genetic model that includes a threshold. One such model assumes that underlying the etiology of a disorder is a continuously distributed variable, *liability,* that encompasses all the endogenous and exogenous factors predisposing to the disorder; the

genetic contributions are assumed to be polygenic. A point along the liability dimension marks the *threshold,* beyond which all individuals are affected. The prevalence of the disorder in the general population defines where the threshold occurs on the liability scale. Falconer provides tables by means of which the prevalence rates of a disorder among relatives of given degrees of relatedness to affected individuals may be converted into an estimate of h^2. Falconer's method has been subjected to various criticisms and alternative threshold models have been advanced, including one involving single genes. Improvements on Falconer's method recently made by Smith have been used to study the genetic basis of schizophrenia.

Despite certain limitations, threshold genetic models have useful predictive properties; they allow the generation of hypotheses that can be tested empirically. For example, such models would predict that:

1. The risks for relatives of an affected individual would be relatively higher for rarer disorders than for more commonly occurring ones. For example, in cleft lip with or without cleft palate, which occurs in the general population at a rate of 0.1 percent, the risks for MZ twins, first, and second degree relatives are respectively, four hundred, forty, and seven times higher than that of the general population. In contrast, in congenital pyloric stenosis among males, with a general population rate of 0.5 percent, the corresponding risks are eighty, ten, and five times higher.

2. The greater the number of affected individuals in a family, the higher the risk for other relatives. This is in contrast to disorders with a simple monogenic basis where the recurrence risk remains constant.

3. Assuming that the severity of a disorder is correlated with the liability above the threshold, the risk for relatives will vary directly with the severity of the disorder in the index case.

4. Where a marked difference occurs in the prevalence of a disorder in the two sexes, relatives of index cases of the less affected sex (= higher threshold) would be at proportionally greater risk than those of index cases of the sex more commonly affected (= lower threshold). For example, stuttering among males occurs at a rate of some three to four times higher than among females. The prevalence of stuttering among fathers and brothers of a male index case are 10.2 and 15.6 percent respectively, whereas for a female index case the corresponding prevalence rates are 33.3 and 26.8 percent.

Methods of Study

Family and twin studies constitute the major research methods of psychiatric genetics. In the former, the incidence of a disorder among the relatives of index cases is compared to the incidence of the disorder in the general population, or to that of a control group. Genetic models predict (1) that the incidence of the disorder will be elevated among relatives of affected individuals over that of the general population and (2) that the relative

incidence of the disorder among the relatives will increase as the genetic relatedness to the index case increases.

In twin studies, comparisons of the degree of similarity are made among monozygotic (MZ) and dizygotic (DZ) groups. Since pairs of MZ twins are genetically alike whereas DZ pairs are no more alike genetically than ordinary siblings, genetic models predict that if genotypic factors are operative in the production of the disorder being studied, then cotwins of affected MZ twins will show a higher concordance or incidence of the disorder than those of affected DZ twins. Concordance rates in twin studies may be calculated on a pairwise or on a casewise (proband method) basis; the latter method generally produces a higher concordance estimate than the former one. The proband method is valid when the members of a concordant twin pair are independently ascertained. Concordance rates in twin studies are also sensitive to sampling procedures. Unsystematic ascertainment and sampling among chronically affected groups, such as resident hospital populations, generally produce a bias toward higher concordance rates among MZ twin pairs than do samples obtained from birth registers or consecutive admissions to an institution. These latter procedures presumably tap a group that is more representative of both the overall twin population and of the general population from which they are drawn.

Twin studies have been criticized in the past on two grounds: (1)

possible inaccuracies in zygosity determination and (2) the possibility that MZ, but not DZ, twin pairs are subjected to systematic treatments that lead to greater intrapair similarity. The availability of multiple blood group polymorphisms, histocompatibility antigens, and dermatoglyphic techniques currently permit the objective diagnosis of zygosity with a high degree of reliability. The second problem cannot be as easily dismissed. Nevertheless, it is of interest that with respect to the major psychiatric disorders, no conclusive evidence is as yet available demonstrating a greater similarity of treatment of MZ twin pairs for environmental factors *relevant* to a given disorder. However, it is generally agreed that supplementary supportive evidence from other sources is preferable to data derived from twin studies alone.

The classical family and twin methods both have difficulties in disentangling genotypic and environmental effects. Recognition of this problem has stimulated alternative lines of research that include:

1. The study of MZ twins reared apart. The number of such twin pairs has generally been too small to shed much light on the etiology of the major psychiatric disorders, although a substantial number have been studied with respect to variations in I.Q. scores.

2. The study of adopted children, born to an affected parent, but raised in homes free from psychopathology.

3. The study of discordant MZ twin pairs, to elucidate the nongenetic factors that distinguish the affected and nonaffected co-twins.

4. High-risk studies of premorbid individuals with an affected relative to elucidate the developmental and predisposing environmental factors that precipitate a given disorder.

Childhood Disorders

Individual differences appear early in life. Direct observation and filmed records of neonate behavior indicate that, from the start, differences exist in the extent to which infants avail themselves of others for the purposes of seeking comfort. Significant variations have been found in the frequency and duration of spontaneous crying and of sucking and mouthing activities, and in the degree to which self- comforting was sought and successfully obtained. Individual differences among neonates also exist in the capacity to take in sensory stimuli. Measures of the frequency and duration of spontaneous visual alertness, of alertness in response to maternal ministrations, of visual pursuit of a moving object, and of responses to sounds all showed variation. Such differences may be major determinants of how infants will experience the world around them; they may, in turn, strongly influence parental responses to the infant. Thus, individual differences at birth may have important consequences for the short- and long-range development of the individual. Needless to say, such variation is not necessarily only genotypic in

origin. Although social influences on neonatal behavioral variation are presumably minimal, pre- and perinatal influences and early life experiences cannot be ruled out as major determinants of early individual differences.

The genotypic contributions to neonatal behavioral variation have not been fully elucidated. However, it is of interest to note that significantly greater intrapair differences were found among DZ infant twin pairs than among MZ pairs in measures of mental and motor activities and of personality, although the extent to which such differences persist is not clear. Comparisons between neonates of differing ethnic background have also shown significant differences on ratings of temperament. Chinese-American newborns have been reported to be less changeable, less perturbable, to calm themselves or to be consoled more readily when upset than those of European-American backgrounds. It has been suggested that some temperamental characteristics in early life may be significantly associated with behavioral disorders later in life.

Mental Retardation

A genetic basis for general intelligence has been firmly established. Studies of MZ twins reared apart invariably indicate that the intrapair correlations of the IQ scores of such twin pairs are significantly higher than those of DZ twin pairs reared together. Within populations, the distribution of

IQ scores forms a bell-shaped curve in conformity with polygenically determined traits. However, toward the lower end of the distribution, a significantly greater number of individuals are actually observed than might be expected. These can be divided into mildly (I.Q. fifty to seventy-five) and severely (I.Q. less than fifty) retarded groups. The former generally constitute part of the normal variation, representing cases of familial retardation. Siblings of such retardates have a distribution of I.Q. scores with a mean around eighty. In contrast, the mean I.Q. of siblings of severe retardates is no different from that of the general population (i.e., one hundred) suggesting that most cases of severe retardation are the result of extraordinary mechanisms such as inborn errors of metabolism, chromosomal disorders, birth difficulties, and other pre- and perinatal factors. Dewey et al. have suggested that approximately 114 recessive gene loci may be involved in the production of severe mental defects. This is possibly an underestimate.

Among the metabolic disorders associated with mental retardation are those related to the metabolism of amino acids (e.g., phenylketonuria, *PKU*), carbohydrates (e.g., Galactosaemia), lipids (e.g., Tay-Sachs disease), purines (e.g., Lesch-Nyhan syndrome), metals (e.g., Wilson's disease), and steroids (e.g., adrenogenital syndrome). A review may be found in Stanbury et al. Among the chromosomal disorders, autosomal anomalies are often associated with mental subnormality. The major associations with mental retardation are Klinefelter's syndrome (47,XXY) and Down's syndrome (trisomy-21).

PKU remains the prototype of an inborn error of metabolism affecting intellectual function. Although the enzymatic deficiency underlying this disorder has been known for several decades, the specific mechanisms that lead to the severe mental retardation and other behavioral features of the disorder are, as yet, unknown. Disturbance of the transport and metabolism of other amino acids,' a deficiency of serotonin, and incomplete or defective myelination of the CNS, possibly due to a depression in pyruvate metabolism, have all been suggested as possible causes of the mental retardation associated with PKU.

With the application of large scale screening programs among newborn populations, variant forms of hyperphenylalanemia resembling classical PKU have been discovered. These include atypical, transient, persistent, and other variants among which most affected individuals appear to show normal levels of intelligence without low phenylalanine dietary treatment. This literature has been reviewed by Hsia and Blaskovics and Nelson. The incidence of classical PKU and persistent hyperphenylalanemia is about one in thirteen thousand live births of which variants constitute one-third to one-half of the cases. Classical PKU is believed to be transmitted by a single autosomal recessive gene; the mode of inheritance of the variants has not yet been clarified. It appears that persistent hyperphenylalanemia may be due to a third or possibly a fourth recessive allele at the PKU locus or to a separate modifier gene that, in homozygous form, raises the phenylalanine level in

individuals who are heterozygous at the PKU locus.

Offspring born to PKU mothers and normal fathers are heterozygous at the PKU locus and would thus be expected to be intellectually normal. Nevertheless, they appear to be at particularly high risk to intellectual deficits and to various congenital anomalies. Among 101 children born to twenty-nine PKU mothers, eight had PKU, twenty-two were of uncertain status and of the remainder, only three were considered to be normal. Infants born of variant mothers, however, do not appear to have a higher than average risk for being retarded, suggesting that the exposure of the fetus to concentrations of phenylalanine above fifteen to twenty mg. per one hundred ml. may interfere with normal developmental processes, resulting in congenital malformations, microcephaly, and mental retardation.

In recent years, attention has begun to be paid to the psychosocial factors affecting the behavioral and intellectual concomitants of PKU. In a study of thirty PKU children, a significant decrease in IQ score and an increase in the incidence of serious behavioral pathology was found among the sixteen children who had experienced immobilization and sensory restrictions during the first three years of life.' If confirmed, such findings may have important implications for the management of affected individuals and the counseling of their families. Although behavioral deficits may owe their *origin* to an underlying metabolic abnormality, intrafamilial and other social factors

appear to promote, maintain, exacerbate, or diminish the intellectual deficits and behavioral symptoms actually measured.

A recently described metabolic defect associated with behavioral dysfunction is the Lesch-Nyhan syndrome, the symptoms of which consist of hyperuricemia, mental retardation, spastic cerebral palsy, choreoathetosis, compulsive self-mutilation, and aggressive behavior. This disorder follows an X-linked recessive mode of transmission and is associated with a deficiency of hypoxanthine-guanine phosphoribosyltransferase, an enzyme involved in purine biosynthesis. More than eighty cases have been described worldwide.

In a study of five children, ranging between nine and fifteen years of age, the presence of varying degrees of retardation was found. Accurate assessment of the mental status of these children was difficult because of the presence of disabilities affecting speech. Nevertheless, with persistent encouragement, the children often made successful efforts to be understood and appeared eager to relate to anyone who showed an interest in them. The self-mutilative behavior of these children began before age two, often following or closely related to a traumatic episode the child had experienced. In four of the children the lips and tongue were the focus of the self-mutilative activity; finger biting appeared to develop later, before the age of five. (In other affected children severe head banging, eye gouging, and picking at open wounds has also been described.) Although most of the self-

mutilation appeared to be involuntary and unpredictable, some of the children clearly used such activities for manipulation and secondary gain and in response to environmental cues. Outwardly expressed aggression often took the form of verbal and physical abuse that appeared to be purposeful. Dizmang and Cheatham comment:

> [these] . . . children are in restraints much of the time and they are often intellectually far more capable of interacting with the world than their motor ability will allow. Their pinching, biting and foul language all appear to be learned behavior that is likely to get a reaction out of the people around them. It did not have the same compulsive quality that the finger and lip biting did.

Further careful observation of Lesch-Nyhan children might elucidate the factors underlying the development of the specific behavioral symptoms involved in this disorder and suggest methods of treatment, in addition to dietary and other biochemical interventions. Similar considerations are surely applicable to other metabolic and chromosomal disorders.

Learning Disorders

The high prevalence rates of learning disabilities in the general population suggest that they comprise a constellation of disorders of major significance. Indeed, they constitute a substantial fraction of the problems requiring psychiatric intervention in the preadolescent and adolescent years. The association of these disorders with scholastic underachievement and

with impulsive and aggressive behavior makes affected children high-risk candidates for more severe behavioral problems later on. The costs of these disorders to the individual, his family, and to society are incalculable.

Illustrative of these disorders, minimal brain dysfunctions (MBD) and developmental dyslexia, will be discussed here. The evidence for genotypic contributions to these disorders is by no means unequivocal. Each diagnostic category appears to encompass a heterogeneous group of related disorders with multiple etiologies: environmental contingencies play a major etiological role. Nonetheless, in each, the evidence for genotypic involvement is suggestive. Each shows a decided familial concentration and, where twin studies are available, concordance rates among MZ twins generally exceed those among DZ pairs. Invariably, males are affected at higher rates than females. Investigators should keep the possibility of a genetic threshold model in mind and provide a breakdown of their data for the two sexes separately in future studies. Also, investigators should be alerted to cases of adopted children and discordant MZ twin pairs, since both would be invaluable research material for the elucidation of the etiological factors underlying these disorders.

MBD encompasses a variety of persistent behavioral problems generally marked by motor hyperactivity, excess distractibility, poorly controlled behavior, and scholastic underachievement in children whose overall

intellectual ability otherwise appears adequate. Among the disorders of childhood, MBD is believed to be the single most common one seen by child psychiatrists. These disorders may occur at a prevalence rate of between 4 and 10 percent' among grade- school children; the rate among males is three or more times higher than among females. Most MBD children develop their symptoms before they enter first grade: close to half may begin to behave abnormally before age one. In half or more of hyperactive children, the symptoms tend to diminish or disappear in later years.

Difficulty exists in the diagnosis of these disorders since hyperactivity may be associated with other behavioral problems including neurologic dysfunction, emotional disorders, and intellectual subnormality. The majority of MBD children appear to have no major detectable neurological abnormalities. However, an increased rate of minor or “soft” neurological signs may be present.

Lopez studied ten pairs of hyperkinetic twins, ranging between five and twelve years of age. All of the four MZ pairs but only one of the six DZ pairs were concordant. All of the concordant MZ pairs were males and, among the discordant DZ twins, the affected co-twin was a male in all but one instance. However, since most of the DZ group consisted of opposite-sexed pairs, no conclusion can be drawn about a genotypic etiology for hyperkinesis on the basis of these data.

The evidence for a familial concentration of MBD is scanty. A retrospective study of the parents and second-degree relatives of a group of hyperactive children revealed that a greater number of these relatives had hyperactive symptoms as children than the relatives of a matched control group. However, the presence of alcoholism, sociopathy, and hysteria among the relatives of the MBD children confounded the possible contributions of genotypic factors. No large-scale attempts to separate the biological, social class, and intra- familial environmental components of MBD have been reported. However, in a study of foster-home-reared sibs and half-sibs of MBD children it was found that about 47 percent of the full sibs exhibited repeated behavior problems, including hyperactivity, whereas only 23 percent of the half-sibs were so characterized. The greatest likelihood of receiving a diagnosis of MBD occurred in those children who had, in addition to a relatively high genetic loading, a low IQ and/or a developmental history of seizures, low birth weight, perinatal complications and congenital malformations. No increased rate of chromosomal abnormalities has been found among MBD children. A comprehensive discussion of the epidemiology, etiology, diagnosis and treatment of MBD has recently been published.

Dyslexia is a ". . . disorder manifested by difficulty in learning to read despite conventional instruction, adequate intelligence, and sociocultural opportunity." Although it was once believed that dyslexia was restricted to individuals of English-speaking nations, it now appears that this disorder may

occur worldwide, including China, India, and Japan. Recent estimates of the prevalence of dyslexia in the general population of Europe and of the United States range from 1 to 35 percent; the modal rate is about 10 percent, indicating that dyslexia is a problem of major magnitude.

Owen et al. have recently reviewed the twin studies of dyslexia. Among a total of twelve MZ twin pairs in three separate studies, all were reported as concordant whereas only a third of the thirty-three pairs of DZ twins were concordant. Unsystematic sampling may account for the high MZ concordance rate.

Evidence for a familial concentration is summarized by Critchley. Hallgren found that 89 percent of 116 index cases had a positive family history of dyslexia. Most of the index cases (81 percent) were found to be members of families with one affected parent. In his study, there was no evidence of increased parental consanguinity or birth-order effects. However, youngest or last-born children have been reported to be at greater risk for dyslexia than older ones. A recent study of fifty adult dyslexics showed that 34 percent had other family members with similar problems.

Hallgren has suggested that dyslexia may be transmitted by a single dominant gene. However, a simple dominant mode of inheritance is complicated by a disproportionate incidence of dyslexia among males; the

incidence is between three to four times greater than among females. Partially this might be due to an ascertainment bias: boys with poor reading abilities may create greater disturbances in school and may be brought to the notice of teachers, parents, and reading clinics more often than girls. Critchley discounts this possibility because of the consistency with which the differential sex difference is found. Hallgren's data might be compatible with a threshold genetic model. In his study, male relations of a proband had a relatively greater risk for dyslexia than female ones. Among the male probands with one affected parent, either parent was likely to be affected (thirty-five fathers and thirty-three mothers were diagnosed as dyslexic). However, among the female probands twice as many fathers (fifteen) as mothers (seven) were affected.

Childhood Psychosis

The psychotic disorders of childhood have been reviewed by Rutter and by Rosenthal. Among these disorders, those with a relatively early age of onset have tended to be distinguished from those involving regression at later ages of onset. The former group—variously called Kanner's syndrome, infantile autism, infantile psychosis, or early childhood psychosis—generally begins before the end of the second year of life, many of the children appearing withdrawn virtually from birth. These early disorders are characterized by autism, marked by aloofness and distance from other

people, speech abnormalities, and ritualistic and compulsive behavior. The prevalence of childhood psychoses may be between 3.1 and 4.5 per ten thousand children; estimates for infantile autism vary from 0.7 to 2.1 per ten thousand. Males appear to be affected two to four times more often than females. Kanner and others have found that first-borns are overrepresented among early onset psychotic children. However, Wing has reported that in large families there may be a tendency for the affected child to appear late in the birth order. Several writers have suggested that a disproportionate number of parents of early onset psychotic children come from well-educated and higher socioeconomic groups and are cold and obsessive in personality. However, these personality characteristics have been disputed: parental abnormalities, if present, might be consequences of their reactions to an abnormal child.

Since the disorder is rare, the number of twins studied has been small; Rutter provides a critical review of these data. After excluding those pairs in which major physical disabilities were present, a total of eleven out of thirteen MZ and one out of four DZ pairs has been reported to be concordant. However, among these studies, satisfactory evidence of zygosity and sufficient clinical details to substantiate the diagnosis were given for only four twin pairs (two MZ and two DZ). Among these, half of each group showed concordance, insufficient to demonstrate a genetic basis unequivocally for the disorder. On the other hand, although the rate of early onset psychosis among

the siblings of affected children is low (approximately 2 percent), it nevertheless appears to be between fifty and one hundred times higher than that of the general population. In general, cytogenetic studies have failed to show the presence of an increased rate of chromosomal anomalies among children with early onset psychosis.

The rate of schizophrenia among the first- degree relatives of early onset psychotic children has been reported to be no higher than that of the general population. In contrast, the rate of schizophrenia among the relatives of children with psychoses with later onset is as high or higher than that found among relatives of adult schizophrenics, suggesting that the late onset group may have a biological unity with adulthood schizophrenia, whereas the early onset group constitutes a genotypically different group of disorders. Goldfarb, however, has pointed out that sampling procedures might account for these apparent differences. Although only 2 percent of the parents in his study were hospitalized for psychiatric reasons, psychiatric evaluations revealed that a diagnosis of schizophrenia was applicable to 29 percent of the mothers and 13 percent of the fathers of the affected children. When the children in his study were subdivided into those with apparent neurological impairments (organic) versus those without (nonorganic) the rates of schizophrenia among the parents of the latter group were 44 and 8 percent for the mothers and fathers respectively whereas the corresponding rates among the “organic” group were 21 and 15 percent. Whether the relatively

higher rate of diagnosed psychosis among the mothers of the nonorganic group represents the effects of predisposing genotypic factors is at present speculative. Also, the differential rates of psychosis in the two sexes among the parents in Goldfarb's study need to be explained. If this sex difference is confirmed, it might suggest that early onset childhood psychosis is unrelated to adult schizophrenia, since no differential sex difference among affected individuals or their parents has been shown in the latter disorder.

Clearly, the biological relationship between early and later onset forms of childhood psychosis and between the former and adult schizophrenia requires further study. Since Goldfarb's sample consisted of individuals predominantly from lower socioeconomic classes, whereas previously reported samples were generally biased in the opposite direction, greater attention to socioeconomic variables is needed, although a recent report suggests that the incidence of autism is not correlated with parental social class. Also, attention needs to be paid to pre- and perinatal factors in relation to early onset childhood psychosis as several investigators have reported an association between pregnancy complications and childhood psychosis.

Adult Disorders

Alcoholism

Although precise estimates are not available, alcoholism in the United States is believed to involve between 4 to 5 percent of the general population. The rate among men may be up to ten or more times higher than among women. Several studies suggest that hereditary factors are operative in the etiology of alcoholism. The pertinent literature is reviewed by Rosenthal and by Goodwin. Invariably, the rate of alcoholism among relatives of alcoholic probands is higher than that of the general population. Also, twin studies generally show that MZ pairs are more similar in their abuse of alcohol and in their drinking habits than DZ pairs. However, the evidence is not unequivocal. If the social consequences of alcohol consumption are used as criteria of alcoholism, then MZ and DZ twin pairs do not appear to differ. Also, in groups of individuals separated from their biological parents early in life and reared in foster homes, no significant differences in problem drinking were found between children born to alcoholic parents and children born to nonalcoholic ones. In fact, none of the former children were alcoholics.

Recent studies suggest that male relatives of a female proband may have a higher risk for alcoholism than those of male alcoholics. Relatives of female alcoholics also appear to show a higher prevalence of depressive disorders than those of male probands. On the other hand, the rates of schizophrenia, mental deficiency, manic-depressive illness, and epilepsy among the relatives of alcoholics do not seem to be increased above their respective rates in the general population.

In a recent study of half-sibs of sixty-nine alcoholic probands, it was reported that the presence of alcoholism in the former was strongly associated with alcoholism in the biological parent. However, the significance of these findings is obscure since the rate of alcoholism among the half-sibs was as high as that among the full sibs despite the fact that the two groups share, on the average, different proportions of their genes in common with a proband. Although an X-linked mode of transmission for alcoholism has been advanced by some, there is little supporting evidence.

In the context of a clinical and pharmacological problem, genotypic influences on the development of tolerance to and physical dependence on alcohol may have an important bearing on the issue of alcohol addiction. ' In this regard it has been reported that a wide range of individual differences exist in the rate of metabolism of an administered dose of alcohol. Intrapair differences in the rates of alcohol elimination from blood plasma were significantly greater among healthy, nonmedicated DZ twin pairs than among MZ pairs; the degree of genetic determination was estimated as 0.98, suggesting that genotypic factors might account for most of the phenotypic variation. Although different ethnic groups require a comparable quantity of alcohol per unit of body weight to reach intoxicating blood levels, some groups metabolize alcohol significantly slower than others and take longer to recover from an alcoholic debauch. Wolff has recently suggested that differences in autonomic nervous system responsivity to alcohol, which

appear to be present at birth, may account for variations of alcoholism rates among different ethnic groups. The extent to which such differences actually contribute to the etiology of alcoholism requires further study. Current research on the biological and environmental factors involved in alcoholism is discussed in a recent publication.

Criminality

The belief that heredity plays a role in the etiology of criminality is an old one. Criminality shows a familial concentration. Also, several twin studies in various countries have shown that the concordance rates for criminality among MZ twin pairs are higher than those among DZ pairs. However, inadequate sampling procedures, questionable determination of zygosity, lack of double-blind assessments, and the failure to separate environmental from hereditary influences render these latter studies equivocal with respect to the demonstration of a genotypic involvement. The causes of violent behavior are complex and although age, sex, and racial differences have been documented, no convincing evidence exists to link these variations to biological and genetic differences. A comprehensive review of the pertinent literature may be found in a recent staff report to the National Commission on the Causes and Prevention of Violence.

In recent years, attention has been directed to the possibility that

individuals with an extra Y chromosome are liable to hyperaggressivity and criminality. It seemed reasonable to suppose that since the relative rates of violent crimes are substantially higher among males than among females, and since males normally carry a Y chromosome, a double dose of this chromosome would increase or exaggerate those masculine characteristics which might lead an individual into conflict with the law.

The first 47,XYY male was detected in 1961. He was described as a physically normal man, six feet in height, of average intelligence, and father of seven living children from two marriages. He was not a criminal; it was the presence of mongolism and other congenital anomalies among his progeny that led to his identification. Between 1961 and 1965, twelve more 47,XYY cases were found, the majority with various physical abnormalities. In 1965, Jacobs and her colleagues and then Price and Whatmore reported on a chromosomal survey of virtually all the male patients of a maximum security state hospital located at Carstairs, Scotland. Of a total of 315 men studied, 9 (2.9 percent) were found to have a 47,XYY karyotype. Since the publication of these reports more than one hundred other 47,XYY individuals have been identified in various prisons and mental hospitals and well over fifty cases have been detected in newborn and adult population surveys, fertility clinics, and private medical practice. The literature is reviewed by Court Brown and others.

Jacobs et al. suggested that 47,XYY males tend to be tall. In the Carstairs group, the mean height of the 47,XYY individuals was 181.2 cm. whereas that of the chromosomally normal inmates was only 170.7 cm. Since many other institutionalized 47,XYY individuals have been ascertained on the basis of height, it has been difficult to confirm the initial findings. There may be a bias on the part of the courts towards the institutionalization of tall offenders. Moreover, tall institutionalized 47,XYY men may come from families with a tendency toward tallness. On the other hand, of twenty-three 47,XYY cases ascertained on a basis other than height half were at least six feet tall.

The evidence for intellectual deficits associated with an extra Y chromosome is difficult to assess since most tested 47,XYY individuals were identified in institutions. Average and above average I.Q. scores have been reported in some cases. Also, in studies where 47,XYY individuals were matched to chromosomally normal controls, no significant differences in mean I.Q. were found.

In their initial report, Price and What- more pointed out that the nine 47,XYY individuals were actually *less* openly hostile and violently aggressive than the eighteen men in a chromosomally normal control group. Although the convictions for crimes against property were proportionally the same in both groups, the 47,XYY individuals showed a significantly lower incidence of crimes of violence than did the controls (8.7 as against 21.9 percent). These

findings suggest that the initial characterization of 47,XYY male as an uncontrollably aggressive psychopath was somewhat exaggerated. If these men are unusually impulsive and/or aggressive, it might be expected that a disproportionate number of 47,XYY males would be found among groups of individuals identified as hyperaggressive on personality tests and other reasonable criteria. All work based on this hypothesis, however, has shown negative findings.

It has also been suggested that the criminal activity of 47,XYY males begins at an early age and that a familial predisposition to criminality is absent. In the Carstairs group the mean ages at first conviction for the 47,XYY individuals and the 46,XY controls were 13.x and 18.0 years respectively. There was only one conviction reported among the thirty-one siblings of the 47,XYY individuals, whereas 139 convictions were found among the sixty-three siblings of the control group. Kessler and Moos provide a critique of this evidence. Suffice it to say that subsequent reports have confirmed neither assertion; several studies show no differences between 47,XYY inmates and 46,XY controls with respect to age at first conviction, and it is now clear that many institutionalized 47,XYY males do come from homes that show evidence of interpersonal or psychosocial disturbance.

With respect to a variety of physical and physiological measures, 47,XYY individuals show a broad range of expression. The evidence appears to

suggest that abnormalities in these measures may occur in a fraction, but not in the majority of these males. Studies of plasma and urinary testosterone levels in 47,XYY individuals are of particular interest since androgens are associated with aggressive behavior. Elevated androgen levels might provide a potential mechanism through which the additional Y chromosome might promote behavioral changes, possibly arising or being exacerbated at the time of puberty. However, several studies have shown no significant differences in testosterone levels between 47,XYY males and 46,XY fellow inmates.

A question that needs further clarification is whether or not 47,XYY individuals have a greater than average risk for criminality. The frequency of 47,XYY males in the newborn population is believed to be approximately 1.8 per one thousand whereas their frequency in certain institutions may be as much as twenty times higher. It is unclear at the present time whether this elevated rate represents sampling bias, random sampling variation, or the reflection of a true predisposition to institutionalization as a consequence of having an extra Y chromosome. In the most extensive and systematic survey thus far reported, Jacobs et al. examined the chromosomes of 2,538 males in a variety of penal and other corrective institutions in Scotland and found that the frequency of 47,XYY males in these institutions was not significantly different from the rate expected on the basis of the newborn incidence.[3] If this finding is confirmed, it would suggest that no increased risk for

criminality may be attached to this chromosomal disorder.

In sum, the evidence suggesting an association between the 47,XYY karyotype and a predisposition to antisocial behavior is inconclusive at the present time. The characterization of the 47,XYY male as uncontrollably hyperaggressive has not been substantiated and, with the possible exception of a tendency to increased stature, no specific behavioral, morphological, or physiological characteristic has emerged differentiating these individuals from males with other chromosomal constitutions.

In a recent report, a higher rate of mental illness and psychopathy was found among the biological relatives of a group of psychopathic adoptees than among the relatives of a matched control group. Preliminary results of another adoption study has recently appeared. Further study is needed since other reports show no clear-cut relationship between the social adjustment of adoptees and the presence of alcoholism or criminality among their biological parents.

Homosexuality

Accurate estimates of the prevalence of homosexuality are not available. Kinsey reported that 37 percent of American males have homosexual experiences involving orgasm during some period of their lives; about 4 percent remain exclusively homosexual throughout their lives. Kenyon

suggests that homosexuality among adult females occurs at the rate of one in forty-five in England.

The literature bearing on possible genotypic contributions to homosexual behavior has been reviewed by Money and others. Most of the evidence derives from twin studies that generally show a higher concordance rate among MZ twin pairs than among DZ pairs. However, the samples, with one exception, were small, were gathered by means of questionable sampling procedures or were otherwise biased to include mostly individuals seeking or requiring psychiatric attention. Whether such samples are representative of homosexuals in general is not known.

Evidence in a different vein, reviewed by Slater and Cowie, suggests that a preponderance of brothers may be present among the sibs of male homosexuals and that homosexuals tend to be born late in the sibship to older mothers. These findings suggest that a chromosomal disorder might be involved in the etiology of homosexuality. However, attempts to find such disorders have not been fruitful. Abe and Moran have shown that the shift in maternal age is secondary to a concomitant shift in paternal age, further ruling out a chromosomal disorder associated with late maternal age as contributing to the etiology of homosexuality.

In sum, the extent to which genotypic factors are involved in the

etiology of homosexual behavior is not clear. Recently, several laboratories have reported striking endocrine differences between homosexuals and nonhomosexuals. The most impressive report to date is that of Kolodny et al. who studied thirty male homosexual university student volunteers and fifty heterosexual male student controls. The plasma testosterone concentrations and sperm counts among the homosexuals showed a graded decrement correlated with the degree of homosexuality, as rated on the Kinsey scale. The mean plasma testosterone concentrations of the subjects rated as Kinsey five and six (almost exclusively and exclusively homosexual) were significantly lower than that of the control group. Whether these differences are related to the pathogenesis of homosexuality or are the secondary results of a homosexual psychosocial orientation needs to be investigated. The possibility that gene- determined differences in the synthesis, transport, and metabolism of androgens may predispose some individuals toward a homosexual orientation should also be explored.

Affective Disorders

Published estimates of the prevalence of the affective disorders vary widely from country to country and at different periods of time even within a single country. Estimates of manic-depressive illness in the general population range from 0.21 percent to close to 5 percent; in British and Scandinavian populations an expectation of about 1 percent is a generally

accepted figure. Differences in the criteria used in the diagnosis of the affective disorders at various clinical centers probably account for the variation in prevalence rates. Most investigators in Western countries report a relatively higher incidence of affective disorders among females than among males; the ratio of females to males in the general population, averaged over several studies, is about 1.5:1.

The evidence suggesting genotypic contributions to the etiology of the affective disorders comes from twin and family studies and is summarized by Slater and Cowie and others. The average concordance rates for manic-depressive psychosis among MZ and same-sexed DZ twin pairs, in several studies, are about 68 and 23 percent respectively. Estimates of the morbid risks for affective disorders among the relatives of manic-depressive probands, averaged over several studies, are shown in Table 17-1. Among the first degree relatives of affected probands the average morbid risk for affective disorders is about 14 percent, a substantial increase over the general population rate. Among second and third degree relatives, average risks are 4.8 and 3.6 percent respectively.

Table 17-1 Morbid Risks for Affective Disorders Among Relatives of Manic-Depressive Probands (in percent).
(Data from Zerbin-Rudin and Slater and Cowie)

	NUMBER OF INVESTIGATIONS	RANGE	MEAN
Parents	9	7-23	14.3

Children	6	8-24	14.8
Sibs	10	4-23	12.9
Half-sibs	2	1-17	9.0
Nieces and Nephews	2	2-3	2.6
Grandchildren	2	1-4	2.5

In recent years, attempts have been made to refine the nosology of the affective disorders. Leonhard et al. and subsequent workers have suggested that depressive illness may be divided into two groups. In one (bipolar psychosis) individuals exhibit episodes of mania or hypomania and depression whereas in the other (unipolar psychosis) only episodes of depression occur. Disagreement exists as to whether these groups constitute genetically distinct entities. Perris found that the morbid risks for bipolar and unipolar psychosis among the first-degree relatives of 138 bipolar probands were 16.3 and 0.8 percent respectively whereas among the relatives of 139 unipolar probands the morbid risks were 0.5 and 10.6 percent respectively for bipolar and unipolar psychoses. These data support the possibility of genetically distinct subtypes. Other workers, however, have reported relatively high rates of unipolar psychosis among the relatives of bipolar probands, indicating that overlap of the two types of disorder exists.

The bipolar-unipolar distinction has been found to be a good one for the purpose of research into the clinical, psychophysiological, and

pharmacological correlates of the affective disorders. The age of onset of bipolar psychosis tends to be earlier than that of the unipolar form, and the morbid risk for affective disorder appears to be higher among the relatives of a bipolar proband than among those of a unipolar one. Depressed bipolar patients have been reported to exhibit less pacing behavior, overt expressions of anger, and somatic complaints than unipolar ones. In contrast to the latter, the former tend to have a lower threshold for flicker stimulation and an augmenting pattern in their measured-average, evoked-cortical potentials. Lithium carbonate appears to be a more effective antidepressant in bipolar patients than in unipolar ones. The former, in contrast to the latter, tend to show hypomanic episodes when treated for depression with L-Dopa, or with tricyclic antidepressants. Red blood cell catechol O-methyltransferase(COMT) activity appears to be relatively lower among unipolar female patients than bipolar ones whereas blood platelet monoamine oxidase (MAO) activity appears to be relatively lower in bipolar patients. Taken together, these findings support the bipolar-unipolar dichotomy and suggest that the differentiation may be a consequence of different underlying genetic systems. Support for this hypothesis derives from data collected by Zerbin-Rudin, who carefully examined the relevant twin literature and found that concordant MZ pairs were, with only a few exceptions, similar as to subtype.

Angst and Perris found an increased number of affected females among the first- degree relatives of unipolar probands whereas among the relatives

of bipolar probands the two sexes were equally affected. Data summarized by Winokur and his coworkers suggest that a preponderance of affected female relatives may occur in families of both bipolar and unipolar female probands. These latter workers have suggested that among the relatives of female bipolar probands affected parents and children show equal proportions of females and males, but affected sisters appear to be some three times more prevalent than affected brothers. They also point out that mothers of male bipolar probands appear to be more often affected than fathers. These findings are suggestive of an X-linked dominant mode of inheritance for bipolar psychosis. In support of this hypothesis, evidence has been advanced suggesting linkage between manic-depressive disorder and the color blindness and Xg blood group loci. However, the number of families involved in the linkage study was small and data of both Cadoret and Winokur and other workers are not consistent with X-linkage. In two recent reports, the distribution of secondary cases of bipolar psychosis between the maternal and paternal sides of the families of bipolar probands was found to be more in accord with a polygenic mode of transmission rather than one involving a major gene.

Winokur and his coworkers have suggested that there may be two groups of unipolar psychosis, one with a relatively early age of onset in which relatively higher morbid risks for depression occur mostly among females and the other with a relatively later age of onset in which female and male

relatives of male probands share equal morbid risks for depression. Perris has argued for a polygenic mode of transmission for unipolar psychosis. Another possibility that has been advanced is that the predisposition to affective disorders may have a heterogeneous genetic basis. The possible association of the affective disorders with aspects of biogenic amine metabolism suggests that pharmacogenetic approaches might be worthwhile in elucidating the apparent genotypic and phenotypic heterogeneity of these disorders. Genetic variation in the metabolism of antidepressant drugs has been found.

Schizophrenia

Evidence pointing to the involvement of genotypic factors in the etiology of schizophrenia has been considerably strengthened in recent years. Eleven major twin studies of schizophrenia have been carried out worldwide: all show higher rates of concordance among MZ than DZ twin pairs. In the older studies, MZ concordance rates are generally 60 percent or more whereas in those conducted after 1965, shown in Table 17-2, average MZ concordance is between 34 and 46 percent. The differences probably reflect the nature of the population studied as well as variations in sampling and statistical procedures. The older studies generally involved chronically affected resident hospital populations whereas the recent ones employed consecutive admissions or birth registers. Of the older twin studies,

Kallmann's is probably the best known because of the large sample (691 pairs) studied, its inordinately high age- corrected MZ concordance rate (86 percent) and the intensity of criticism it received. In their study, Gottesman and Shields took account of many of the criticisms of the diagnostic and sampling procedures of the earlier twin studies. Their study was organized prospectively and consisted of a sample of consecutive admissions to a short-stay psychiatric hospital over a period of sixteen years. Both sexes were represented equally among the probands and zygosity was carefully determined. These investigators found that without age-correction 42 percent of the twenty-four MZ pairs and only 9 percent of the thirty- three same-sexed DZ twin pairs were concordant for schizophrenia. To study the effect of differential diagnostic criteria on concordance rates, summaries of the case histories of the 114 individual twins were submitted to six clinicians from three different countries representing a broad range of psychiatric orientation. Each judge, blind as to diagnosis and zygosity, arrived at his own diagnostic assessment. In sum, it was found that despite individual diagnostic preferences considerable agreement existed among the judges. The consensus diagnosis yielded concordance rates similar to those found by Gottesman and Shields in their original study. Of particular interest was the fact that neither narrow nor broad concepts of schizophrenia but rather middle-of-the-road diagnostic criteria produced the most reliable discrimination between MZ and DZ concordance rates, and hence the highest

estimate of heritability.

Table 17-2. Concordance Rates in Recent Twin Studies of Schizophrenia (in percent).

	MZ TWINS			DZ TWINS		
	N *(pairs)*	*(a)*	*(b)*	N *(pairs)*	*(a)*	*(b)*
Kringlen (1968) Norway	55	25-39	45	90	7-10	15
Fischer et al. (1969) Denmark	21	24-48	56	41	10-20	26
Tienari* (1971) Finland	19	16	35	34	3	13
Allen et al.* (1972) U.S.A.	95	27	43	125	5	9
Gottesman and Shields (1972) U.K.	24	42	58	33	9	12

(a) pairwise concordance

(b) proband method (from)

* Only male pairs studied.

Studies of MZ twin pairs reared apart also suggest that genotypic factors are involved in the etiology of schizophrenia. Of the seventeen such pairs compiled by Slater and Cowie, eleven (65 percent) were reported to be concordant for schizophrenia. However, more than half of these pairs were not obtained in a systematic way, and, thus, discordant pairs may have been underreported.

Schizophrenia shows a decided familial concentration (Table 17-3). The median morbid risk for schizophrenia in the general population, derived from nineteen studies tabulated by Zerbin-Riidin, is about 0.8 percent. Both sexes appear to be equally at risk. Among the first-degree relatives of an affected proband, the median risk over all studies is about 8.6 percent; for second- and third- degree relatives, the risks are 2.1 and 1.7 percent respectively. Thus, there is an elevation of morbid risks for schizophrenia among the relatives of probands over that of the general population, increasing as the degree of genetic relatedness to the proband increases.

Table 17-3. Estimates of Morbid Risks for Schizophrenia Among Relatives of Schizophrenic Probands (in percent). (Data from various sources.)

Parents	4.2-5.5
Children	9.7-13.9
Children (both parents affected)	35-46
Sibs (all)	7.5-10.2
(neither parent affected)	6.7-9.7
(one parent schizophrenic)	12.5-17.2
Half-sibs	3.2-3.5
Aunts and Uncles	2.0-3.6
Nieces and Nephews	2.2-2.6
Grandchildren	2.8-3.5

The most compelling evidence for the role of genotypic factors in the

etiology of schizophrenia derives from the study of adoptive children. Karlsson found that among the relatives of eight schizophrenic probands who were reared by unrelated adoptive parents from the first year of life, six of the twenty-nine biologic sibs and none of the twenty-eight foster sibs were schizophrenic. In another report, Karlsson discusses several other cases of affected individuals born to a schizophrenic parent but separated from them early in life. Heston studied a group of forty-seven individuals (an experimental group) born to hospitalized schizophrenic mothers, but separated from them at birth and reared in foster homes. A control group, selected from fifty individuals who had entered the same foundling homes around the same time as the first group, was matched to the experimentals by age, sex, type of eventual placement (adoptive, foster family, or institutional) and the length of time in child-care institutions. None of the mothers of the controls had a known psychiatric disorder. Most subjects were personally interviewed and information from psychiatric, police, and social- service agencies, private physicians, friends, relatives, and other sources was also obtained.

All the subjects were about thirty-six years of age at the time of the study and were thus well into the age of risk for schizophrenia. It was found that five of the experimental group and none of the controls were diagnosed as schizophrenic. In addition, Heston found significantly lower scores on the Menninger Mental Health-Sickness Rating Scale (MHSRS) and relatively

higher incidences of criminality, mental deficiency, neurotic personality disorder and sociopathic personality among the experimental group than among the controls.

A series of adoption studies have also been carried out by Kety, Rosenthal, and their coworkers in Denmark. From an adoption register of the greater Copenhagen area, the names of approximately fifty-five hundred individuals were obtained who had been given up for nonfamilial adoption at an early age, between 1923 and 1947. From these records the names, addresses, and other pertinent information concerning the biological and adoptive parents were also obtained. From a psychiatric register and other sources it was possible to determine which individuals had a psychiatric history. In one study, approximately ten thousand parents of the adoptees were considered. The hospital records of the parents listed in the psychiatric register were examined independently, first by Danish psychiatrists and then by the American collaborators. If diagnostic agreement was reached, the child given up for adoption by that parent became an index case. From the remaining adoptees, a group of controls was selected, none of whose biological parents had a psychiatric history. The control and index adoptees were matched for age, sex, age at transfer to the adoptive family, and socioeconomic status of the adopting family. In this way, seventy-six index and sixty-seven control adoptees, with a mean age of thirty-three years, were collected for study. Each received a psychiatric interview, carried out so that

the interviewer was blind as to whether a given individual belonged to the index or control groups. Of the index parents, fifty were mothers and twenty-six were fathers; only ten of the parents had their first psychiatric admission antedating the birth of the index child. It was found that twenty-four (31.6 percent) of the index and twelve (17.8 percent) of the control children had a schizophrenic-spectrum diagnosis;[4] the difference between the two groups is statistically significant. The relative severity of the psychiatric diagnoses was greater among the index cases than among the controls. The three cases with diagnoses of chronic schizophrenia were all index cases.

In a second study, the rates of schizophrenic disorders among the biological and adoptive relatives of a group of index and control adoptees were determined. Among the parents, sibs, and half-sibs of thirty-three affected index cases thirteen out of one hundred and fifty of the biological but only two out of seventy-four of the adoptive relatives had a schizophrenic-spectrum disorder, whereas among the relatives of thirty-three matched controls three of one hundred fifty-six biological and three of eighty-three adoptive relatives were found affected. Thus, although there was no significant difference in the prevalence of schizophrenic disorders among the adoptive relatives of the two groups, the rate of these disorders among the biological relatives of the index cases was significantly higher than that among the controls. Taken together with the twin and family studies, these data strongly suggest that genotypic factors play a role in the development of

schizophrenia.

No widespread agreement exists as to the mode of inheritance of the genes that predispose to schizophrenia. Recent theories include major gene, polygenic, and various mixed or heterogeneity models. Following Kallmann's earlier arguments, Hurst has recently defended a single locus recessive model. Kidd and Cavalli-Sforza have suggested that available family data are compatible with a single recessive having a gene frequency of about 10 percent and a threshold such that 50 percent or more of the homozygous recessives would be affected. Slater, on the other hand, has advanced a model involving a partially dominant gene with a frequency of about 3 percent and with a manifestation rate in the heterozygote of 13 percent. According to this model, most schizophrenics would be heterozygotes. Karlsson has suggested a two-factor model involving a dominant principal gene with a frequency of about 7 percent and a secondary dominant with a frequency between 20 and 30 percent. Other investigators favor a polygenic mode of inheritance. A polygenic threshold model has been advanced by Gottesman and Shields who, following Falconer and Smith, have calculated the heritability of the liability to schizophrenia to be about 85 percent.

Several heterogeneity models have been advanced; these consider the possibility that schizophrenia constitutes a collection of heterogeneous disorders with differing genotypic etiologies. Genetic heterogeneity may arise

as a result of the effects of genes or blocks of genes at different loci or the presence of multiple alleles at a common locus. Morton and his coworkers have shown that for heterogeneous disorders like limb- girdle muscular dystrophy, deaf-mutism, and severe mental defect estimates of the proportion of all cases resulting from major gene effects can be calculated. These workers distinguish two etiological groups, a high-risk group in which the recurrence risk for sibs of affected individuals is appreciable due to the segregation of fully penetrant recessive genes, and a low-risk group of sporadic cases due to mutations, phenocopies (environmentally induced mimics of a genetic disorder) and polygenic complexes in which recurrence risks for sibs are small. For severe mental defect, 88 percent of the cases were found to belong to the sporadic group; the remainder were attributed to a minimum of twenty-two contributory recessive loci. A modified version of this model might be applicable to schizophrenia. However, adequate empirical tests for heterogeneity models of schizophrenia have not yet been developed. It is of interest to note that genetic heterogeneity has become an increasingly common finding in human genetics research.

Arguments for and against the monogenic and polygenic models for schizophrenia are discussed by several writers. Major gene theories generally require auxiliary assumptions of reduced penetrance to account for the inadequate fit of family and twin data to Mendelian expectations, and selective advantages to account for the maintenance of the disorder over time

in the face of the reduced reproductive rate of affected individualists Heston attempted to bypass the difficulty of reduced penetrance by postulating that schizoid disorders and schizophrenia are alternative expressions of a single dominant gene. However, there is poor clinical consensus over what constitutes a schizoid disorder. Moreover, even when the frequency of both disorders is taken into account, the observed rates for all degrees of relationship to an affected individual are consistently lower than those expected on the basis of a fully penetrant, single dominant gene.

To account for the apparent maintenance of the genes predisposing to schizophrenia over time, some workers have suggested that heterozygotes enjoy selective advantages that lead to the maintenance of a balanced polymorphism. Moran has suggested that a reproductive advantage of about xo percent in nonschizophrenic heterozygotes would be needed to maintain a balanced polymorphism. Several investigators have discussed possible sources of such advantages. Huxley et al. have suggested that schizophrenics may be resistant to surgical shocks and to infections. However, with the possible exception of an increased resistance to viral infections, the evidence is largely unsubstantiated. Erlenmeyer-Kimling found that during the first year of life, infants born to schizophrenics have a lower mortality rate than same-sexed infants in the general population. Female offspring of a schizophrenic parent were found to have a significantly lower mortality rate during the period from birth to age fifteen than did females of the general

population. If confirmed, these findings would provide some support for the possibility that the genes associated with schizophrenia confer sufficient compensatory advantages on their carriers to maintain a balanced polymorphism. Bodmer has suggested that a polymorphism could be maintained through a higher relative reproductive rate among the unaffected relatives of schizophrenics. Study of the marriage and fertility trends in schizophrenic patients admitted to state hospitals in New York State revealed that over the past few decades the reproductive disadvantages of schizophrenics have declined. Of particular interest is the fact that the reproductive rate of nonaffected sisters of schizophrenics increased, during a twenty-year period, to X40 percent that of the general population rate. Relevant to these findings are suggestions that nonschizophrenic relatives of affected individuals may be predisposed to creativity, giftedness, resourcefulness, and other desirable behavioral characteristics. If these attributes are associated with the increased fertility of relatives of schizophrenics, it would suggest that the possible long-range dysgenic trends attending changes in the fertility of schizophrenics might be offset by the increase in frequency of adaptive attributes in other individuals.

Polygenic models obviate the necessity of postulating the balanced polymorphism and/ or reduced penetrance required by monogenic models. Available family data appear to support a polygenic model- Edwards has shown that the incidence of a polygenically inherited disorder in first-degree

relatives of probands would approximate the square root of the general population incidence. If the incidence of schizophrenia in the general population is 0.8 percent, then it would be expected that approximately 9 percent of the first-degree relatives of probands would be affected. This accords closely to the median morbid risk for this group of relatives (see Table 17-3). Support for a polygenic threshold model is provided by the relationship between the morbid risks in relatives and the severity of the disorder in the proband. If it is assumed that severely affected individuals carry a greater number of the relevant predisposing genes than more mildly affected persons, it would be expected that the prevalence of schizophrenia among relatives of the former would be higher than that among the latter. Although in one family study no strong relationship was found between measures of severity and the presence of a family history of schizophrenia, in several twin studies the severity of the illness in MZ probands has been found to be associated with the concordance rate in the co-twins. Also, pertinent to the relationship between high risk and severity are data showing that the morbid risk for sibs of affected individuals increases substantially if one parent is also affected (Table 17-3). On the basis of a simple single gene model, the risk for subsequent sibs would be expected to remain constant. However, recently advanced major gene models account for the increase in risk about as well as a polygenic threshold model does.

In sum, available data derived from family and twin studies of

schizophrenia can be fitted to multiple models of genetic transmission. Recent attempts to discriminate between different modes of inheritance in schizophrenia and in other disorders without an obvious Mendelian pattern of transmission suggest that this problem has no easy solution. The one point on which there is agreement is that both genotypic and environmental factors are involved in the development of schizophrenia.

Recent years have seen an increasing interest in MZ twins discordant for schizophrenia. The elucidation of the life-history differences and the biological and psychological variables that differentiate the affected and nonaffected members of MZ twin pairs would contribute to our understanding of the genotype-environment interactions involved in the precipitation of schizophrenia. Such studies might define which variables require greater attention in future research and suggest strategies of intervention that might prevent the development of illness in vulnerable individuals. Stabenau and Pollin have suggested that, in contrast to the nonschizophrenic co-twin, the affected one was more likely to have been weaker, shorter, and lighter at birth, and to have experienced birth complications such as neonatal asphyxia. As a child, CNS illness was also likely. Behaviorally, the affected twin was reported to have been more submissive, sensitive, serious, obedient, dependent, stubborn, and neurotic as a child than the nonschizophrenic co-twin. The schizophrenic twin also tended to be strongly identified with the psychologically less healthy parent

who had a more global cognitive style than did the other parent. Other intrapair comparisons suggest that schizophrenic twins have more abnormal neurological signs, a higher lactate/pvruvate ratio and higher titers of antirabbit heterophile hemagglutinin than their nonschizophrenic co-twins. On the other hand, no significant differences were found in serum S19 macroglobulin levels or in the urinary excretion of 3,4-dimethoxyphenylethylamine (DMPEA) in discordant MZ pairs. Some of the issues that need to be explored in discordancy research are the applicability of detected differences to concordant twins and to nontwin schizophrenic groups; whether the differences are present prior to the onset of illness or develop as a consequence of the psychopathology; the specificity of the differences to schizophrenia; and the effects of systematic manipulations of life experiences, as, for example, through psychiatric attention, on co-twin differences. Some of the intrapair differences detected in discordancy research have not always been found among concordant twin pairs or singletons.

Another important research strategy adopted in recent years is the so-called high-risk approach in which individuals predisposed to schizophrenia and their families are studied prospectively in order to elucidate the biological and psychological factors that precede the onset of schizophrenia and contribute to its precipitation. Wynne has provided a provocative discussion of the various strategies employed in high-risk research. Mednick

and his coworkers pioneered such studies in Denmark; at least eleven other high-risk studies are currently ongoing worldwide. Mednick is studying a group of 207 high-risk children born to chronically and severely schizophrenic mothers matched to a group of 104 (low-risk) controls for age, sex, social class, and other variables. Since the onset of the study in 1962, twenty of the high-risk group have suffered psychiatric breakdown. Each breakdown subject was then matched with a low-risk control. Comparisons of these with another unaffected high-risk subject and three groups have suggested that the mothers of the sick group were more severely schizophrenic and hospitalized earlier than those of the unaffected high-risk children, that the sick children have suffered one or more serious pregnancy or birth complications, and had been considerably more aggressive and disruptive in school than the children of the other groups. Galvanic skin responses (GSR) and responses on a word-association test also appeared to differentiate the sick group from the others. A preliminary report of another ongoing high-risk study being conducted by Anthony has also recently appeared.

Future Avenues of Research

One of the central issues in psychiatric research is the relation between life stresses and behavioral dysfunction. Clinical and experimental observations suggest that differential susceptibility to illness might be a

consequence of how different individuals adapt and respond to stress. Presumably, numerous genotypic and environmental factors contribute to such individual variation. One of the promising lines of research in this area involves studies focused on the intervening hormonal substrates of behavior. Stress affects multiple endocrine systems. Conversely, hormones influence CNS function. Genetic variation affecting the synthesis and metabolism of the andrenocortical and thyroid hormones has been identified. It is conceivable that certain individuals carrying gene defects affecting these endocrine systems may, when subjected to sustained major stress situations, produce deficient or excessive amounts of these hormones or their metabolites, with concomitant adverse effects on CNS functioning. Investigation of the interdigitation of genes, hormones, and behavior may have important implications for psychiatry and psychosomatic medicine.

With the increased use of drugs in the treatment of behavioral disorders, psychopharmacogenetic research opportunities have become available. Suggestions have been made that relatives of depressive patients tend to respond to the same class of antidepressant drug, either MAO inhibitors or tricyclic compounds, in the same way as the proband. No similarity of response was found when antidepressants of different groups were used. In the treatment of schizophrenics with phenothiazines, the risk of extrapyramidal side effects appears to be increased in patients with a positive family history of Parkinson's disease. These and similar findings need to be

explored further. The study of genetically determined differences in the response of individuals to drugs that alter mood and behavior may elucidate some of the biochemical mechanisms underlying behavioral disorders and may contribute to the identification of distinct clinical subgroups among the major psychoses.

Stronger collaborative interactions are needed between biochemists and psychiatric geneticists. Too often biochemical research into behavioral disorder begins by assuming the presence of a genetic etiology, but then proceeds to ignore the implications of that assumption in the specific research carried out. A behavioral-biochemical correlation due to a common genetic cause should show predictable patterns of transmission among relatives of an affected individual. Thus, segregation studies should reveal which correlations continue to hold and which break down among relatives of probands. The former situation would suggest that a common genetic basis is present whereas the latter would show that no genetic relationship exists between the biochemical variable being studied and the behavior. For example, although the protein factor identified by the L/P ratio has been found in greater concentrations in the plasma of schizophrenics than in that of normal people, study of the families of schizophrenics showed that the correlation between schizophrenic symptomatology and high L/P ratio disappears. Thus, whatever is being measured by the L/P ratio probably has little or no etiological relationship to schizophrenia.

Until recently, the history of psychiatric genetics has been marked by an overriding concern with nature-nurture issues, which had as their focus the demonstration of a genotypic influence on behavioral characters and on determining morbid risks and patterns of inheritance. There is a growing awareness of the need to shift the primary focus of psychiatric genetics research to the problem of genotype-environment interactions. Developmental studies should receive strong encouragement. Too little is known about the ontogeny of behavioral dysfunction in children with inborn errors of metabolism and chromosomal disorders. Studies are needed to elucidate the reaction range of a particular genotype or karyotype in differing environments. With respect to the major psychoses, the high-risk strategy has emerged as the approach with the greatest potential of clarifying the complex interplay of genotypic, biochemical, physiological, psychological, and social factors that promote or prevent behavioral disorder in predisposed individuals. Once illness is present, it is virtually impossible to tease apart the etiological variables from those which arise as consequences of the illness. Thus, the prospective, longitudinal study of premorbid individuals, preferably in conjunction with an adoption strategy, is long overdue as a central methodology of psychiatric genetics. In the face of the major contributions of experiential factors to human behavior, such research approaches may yield considerably more appropriate data for genetic analysis than that provided by classical human genetics methodology.

The increasing use of adoption studies in psychiatric genetics research suggests that greater attention needs to be paid to the psychology and sociology of adoption. Adoption may involve something more than an ordinary parent-child relationship. The intriguing possibility advanced by Rosenthal and others that adoption may have ameliorative consequences for the adopted individual needs further exploration. In the adoption study of schizophrenia carried out in Denmark, only 0.3 percent of the total group of fifty-five hundred adoptees were classified as chronic or process schizophrenia. This rate, the lowest ever reported in a Scandinavian population, may be due to several factors. One possibility is that adoptive rearing may contribute to the reduced expression of psychopathology. The fact that the rate of hospitalized schizophrenia (1.3 percent) among the adoptees born to a schizophrenic parent was lower than that reported for offspring of schizophrenics generally is consistent with this possibility.

The rapid advances in scientific technology, particularly those related to prenatal diagnosis and to chromosome identification and mapping, will presumably have important implications for psychiatric genetics as well as for medical practice generally. Taken together with available techniques of manipulating behavior through behavioral and pharmacological means and the future possibilities of modifying behavior through genetic engineering, the potential of controlling and directing man's behavioral evolution is becoming an increasing reality. To what extent and to what ends should

human behavior be manipulated? Underlying these questions are important ethical and philosophical issues concerning the nature of man and the meaning of his existence. Is man beyond freedom, dignity, choice, and responsibility, or are these attributes the core of his existence? Whatever answers eventually emerge, it is clear that both the biological and sociocultural bases of human behavior will need to be taken into account.

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Notes

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2 Major differences exist, however, in the portion of the genome actually active at a given time during the course of life. For example, genes active in the synthesis of fetal hemoglobin (HbF), are inactive postnatally, when HbA is normally formed.

3 Although several reports have suggested that 47,XXY males are also predisposed to criminality, they found no increase in the frequency of these individuals above that of the newborn rate.

4 The schizophrenic-spectrum disorders are described by Kety et al. They include chronic or process, acute and borderline or psychoneurotic schizophrenia, and severely schizoid or inadequate personality.